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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,818	04/12/2001	Pnina Fishman	2786-0170P	1935

1444 7590 11/16/2004

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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 11/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,818	FISHMAN, PNINA	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 36-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I in the reply filed on November 8, 2002 is acknowledged. The requirement was made FINAL in the Office Action dated January 28, 2003.

2. Applicant's species election without traverse in the reply filed on December 23, 2002 is acknowledged.

RCE dated August 30, 2004 (Amendments/Remarks filed July 21, 2004)

3. In the Response filed July 21, 2004, claims 1 and 9 were amended, and claim 38 was added.

4. Claims 1-16 and 36-38 are pending. An action on the merits of claims 1-16 and 36-38 is contained herein below.

5. Applicant's arguments with respect to claims 1-16 and 36-37 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Jacobsen et al. US 5,773,423 (Jacobsen).

Jacobsen discloses compounds which have been found to be selective A_3 adenosine receptor agonists, pharmaceutical compositions containing such compounds, and related treatment methods and assay methods (column 2, line 59 to column 3, line 33). The modification of adenosine at the 5'-position and/or at the N^6-position with groups that enhance A_3 potency has been found to result in moderate A_3 selectivity. In particular, the 5'-methyluronamide modification of adenosine and the N^6-benzyl group, either alone or in combination, increases affinity in binding to A_3 receptors relative to A_1 and A_{2a} receptors. Optimization of substituent groups has led to the development of the highly potent A_3 agonist N^6-(3-iodobenzyl)-adenosine-5'-N-methyluroamide (IB-MECA) which is 50-fold selective for A_3 vs. either A_1 or A_2 receptors. Triple substitution of adenosine results in the further enhancement of the degree of A_3 selectivity. 2-Chloro-N^6-(3-iodobenzyl)-adenosine-5'-N-methyluronamide (Cl-IB-MECA) has been found to be the most potent and selective agent in binding assays and has been shown to be a full agonist in the inhibition of adenylate cyclase. Disease states and conditions that may be chronically treated include inflammatory disorders, Parkinson's disease, cardiac disease, and contraception (column 25, line 20 to column 26, line 19). One skilled in the art will recognize that dosage will depend upon a variety of factors including the strength of the particular compound employed, the age, species, condition, and body weight of the animal, as well as the severity/stage of the disease or condition (column 26, line 61 to column 27,

line 23). The size of the dose will also be determined by the route, timing, and frequency of administration as well as the existence, nature, and extent of any adverse side effects that might accompany the administration of a particular compound and desired physiological effect. There are a wide variety of suitable formulations including formulations for oral, aerosol, parenteral, subcutaneous, intravenous, intramuscular, interperitoneal, rectal, and vaginal administration (column 19, lines 59-67).

Jacobsen is silent as to the activation of natural killer cells; however, artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. In construing process claims and references, it is the identity of manipulative operations which leads to finding of anticipation. In the instant case, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Jacobsen discloses the administration of A_3 receptor agonists such as IB-MECA and Cl-IB-MECA to patients in need of treatment for reproductive and non-reproductive problems. The activation of natural killer cells is not an active methodological step in the process but is rather a consequence of the biological/pharmacological properties of the receptor agonist.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to

> be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 9-16 and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobsen et al. US 5,773,423 (Jacobsen) in combination with Yao et al. *Biochemical and Biophysical Research Communications* (1997), Vol. 232, pages 317-322 (Yao) and Wansbrough *Medical Post* (2000), Volume 36, Issue 06 (Wansbrough).

Applicant claims methods to activate natural killer cells and methods for therapeutic treatment through activation of natural killer cells via an adenosine A_3 receptor agonist. In particular, applicant claims a method for treatment wherein the disease is associated with malignant cells or cells infected with viruses, bacteria or protozoa.

Jacobsen discloses compounds which have been found to be selective A_3 adenosine receptor agonists, pharmaceutical compositions containing such compounds, and related treatment methods and assay methods (column 2, line 59 to column 3, line 33). The modification of adenosine at the 5'-position and/or

at the N^6-position with groups that enhance A_3 potency has been found to result in moderate A_3 selectivity. In particular, the 5'-methyluronamide modification of adenosine and the N^6-benzyl group, either alone or in combination, increases affinity in binding to A_3 receptors relative to A_1 and A_{2a} receptors. Optimization of substituent groups has led to the development of the highly potent A_3 agonist N^6-(3-iodobenzyl)-adenosine-5'-N-methyluroamide (IB-MECA) which is 50-fold selective for A_3 vs. either A_1 or A_2 receptors. Triple substitution of adenosine results in the further enhancement of the degree of A_3 selectivity. 2-Chloro-N^6-(3-iodobenzyl)-adenosine-5'-N-methyluronamide (Cl-IB-MECA) has been found to be the most potent and selective agent in binding assays and has been shown to be a full agonist in the inhibition of adenylate cyclase. Disease states and conditions that may be chronically treated include inflammatory disorders, Parkinson's disease, cardiac disease, and contraception (column 25, line 20 to column 26, line 19). One skilled in the art will recognize that dosage will depend upon a variety of factors including the strength of the particular compound employed, the age, species, condition, and body weight of the animal, as well as the severity/stage of the disease or condition (column 26, line 61 to column 27, line 23). The size of the dose will also be determined by the route, timing, and frequency of administration as well as the existence, nature, and extent of any adverse side effects that might accompany the administration of a particular compound and desired physiological effect. There are a wide variety of suitable formulations including formulations for oral, aerosol, parenteral, subcutaneous,

intravenous, intramuscular, interperitoneal, rectal, and vaginal administration (column 19, lines 59-67).

Jacobsen is silent as to the activation of natural killer cells; however, artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Jacobsen discloses the administration of A_3 receptor agonists such as IB-MECA and Cl-IB-MECA to patients in need of treatment for reproductive and non-reproductive problems. The activation of natural killer cells is not an active methodological step in the process but is rather a consequence of the biological/pharmacological properties of the receptor agonist.

Jacobsen differs from the instantly claimed invention in that Jacobsen does not teach the administration of A_3 receptor agonists such as IB-MECA and Cl-IB-MECA to patients having a disease associated with malignant cells or a disease associated with cells infected with viruses, bacteria or protozoa.

Yao teaches that A_3 agonists such as IB-MECA and Cl-IB-MECA, by virtue of regulating programmed cell death, may have application in treating diseases either in which cytotoxicity is undesirable, such as neudegeneration, or desirable such as cancer and inflammation (page 322, last paragraph).

Wansbrough teaches the association of viruses and breast cancer.

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat a patient having a disease associated with malignant cells

by administering IB-MECA or Cl-IB-MECA to said patient since Yao teaches the usefulness of both agonists for the treatment of cancer as well as inflammation. Yao is silent in regards to the association of cancer and viruses; however, at the time of the invention, it was known in the art that there was a link between cancer and viruses. Yao provides sufficient motivation for practicing the instantly claimed invention.

Conclusion

11. Claims 1-16 and 36-38 are pending. Claims 1-16 and 36-38 are rejected. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on Monday - Friday (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick T. Lewis, PhD
Examiner
Art Unit 1623

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